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Hemostatic resuscitation in patients with trauma-induced coagulopathy: a narrative review

Junsik Kwon, Byung Hee Kang

Division of Trauma Surgery, Department of Surgery, Ajou University School of Medicine, Suwon, Korea

Hemorrhage remains a leading cause of preventable death in trauma, emphasizing the importance of early bleeding control. In addition to mechanical hemostasis, effective management of trauma-induced coagulopathy (TIC) plays a critical role in improving outcomes. TIC is a multifactorial condition with diverse phenotypes, involving complex pathophysiology. These variations complicate early diagnosis and targeted treatment. In the prehospital setting, phenotype-based management is not feasible; thus, empirical strategies have been adopted. Administration of tranexamic acid and prehospital whole blood transfusion have shown clinical benefit in selected trauma populations. Upon hospital arrival, fixed-ratio massive transfusion protocols and whole blood resuscitation provide broad support for coagulopathic states and have proven effective in reducing early mortality. However, these approaches may not fully account for individual variation in coagulation profiles. Viscoelastic assays allow real-time evaluation of coagulation status and offer the potential for individualized, goal-directed therapy. While some studies suggest improved outcomes with viscoelastic-guided resuscitation, evidence of clear superiority over conventional methods remains limited. Further research is needed to determine the optimal resuscitation strategy and integrate both empirical and precision-based approaches in TIC management.

Key Words: blood transfusion; hemorrhagic shock, hemostasis; trauma; resuscitation

Review Article

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Corresponding author
Byung Hee Kang
Division of Trauma Surgery, Department of Surgery, Ajou University School of Medicine, 206 World cup-ro, Yeongtong-gu, Suwon 16499, Korea
Tel: +82-31-219-4457
Fax: +82-31-219-7781
Email: kbhname@aumc.ac.kr

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INTRODUCTION

Trauma remains a leading cause of death, particularly among economically active age groups, with hemorrhage being the primary contributor to early mortality [1]. As a result, trauma care is fundamentally centered around effective bleeding control. Over time, hemostatic resuscitation strategies have evolved to address this critical issue. Direct compression has been and continues to be the most effective method to control bleeding, as demonstrated by the persistence of the tourniquet, developed by Jean-Louis Petit [2]. However, in cases of non-compressible bleeding such as torso injuries, surgical intervention typically is required. Therefore, various resuscitation strategies—including fluid administration, blood transfusion, and hemostatic agents—have been developed to sustain patients until surgical hemostasis

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can be achieved. As a result, modern damage control resuscitation is based on the principles of permissive hypotension to minimize bleeding, damage control surgery to achieve surgical hemostasis, and early blood transfusion to correct coagulopathy [3]. Nevertheless, as our understanding of trauma-induced coagulopathy (TIC) continues to deepen, controversy remains regarding the timing of and appropriate type of blood products or medication to be administered. In this review, we provide an updated overview of the current strategies for hemostatic resuscitation.

KEY MESSAGES

- Early bleeding control is essential in the management of trauma-induced coagulopathy (TIC) and should begin in the prehospital setting.
- Fixed-ratio transfusion is effective but carries a risk of over-transfusion; therefore, it could be used in conjunction with goal-directed therapy.
- TIC presents with variable phenotypes; therefore, individualized treatment guided by viscoelastic assays is recommended during initial resuscitation.

TRAUMA-INDUCED COAGULOPATHY

Coagulopathy is common in severely injured patients with bleeding. In addition, correction of the lethal triad of coagulopathy, metabolic acidosis, and hypothermia is important for a positive outcome. This phenomenon is diagnosed based on symptoms and signs and has had various names, such as "severe bleeding tendency," "defibrination syndrome," and "acute traumatic coagulopathy" [4]. In 2010, the term "trauma-induced coagulopathy" was established during the Trans-Agency Consortium for Trauma-Induced Coagulopathy Workshop conducted by the National Institutes of Health. Various hypotheses have been presented for the mechanism of coagulopathy, such as activation of protein C or a tissue factor, endothelial dysfunction, platelet dysfunction, inappropriate thrombin generation, fibrinogen depletion, and hyperfibrinolysis. This suggests that similar bleeding tendencies can be caused by various mechanisms or depletion phenotypes [5]. On the other hand, TIC could arise from cellular injury that manifests as a hypercoagulation tendency. Hence, such a hypercoagulable state after trauma is a rationale for early thromboprophylaxis after injury. Because TIC is a form of shock caused by acute blood loss or massive tissue injury, hypercoagulopathy is not an initial concern. For this reason, states of "early TIC" (generally within 6 hours of injury), which is characterized by bleeding tendency, and "late TIC" (usually >24 hours after injury), which is represented by a hypercoagulable state, have been suggested. However, such disease progression can occur over a wide range of time, from minutes to days (Figure 1) [6].

In conclusion, although the clinical manifestations are diverse, and no consensus definition has been established,

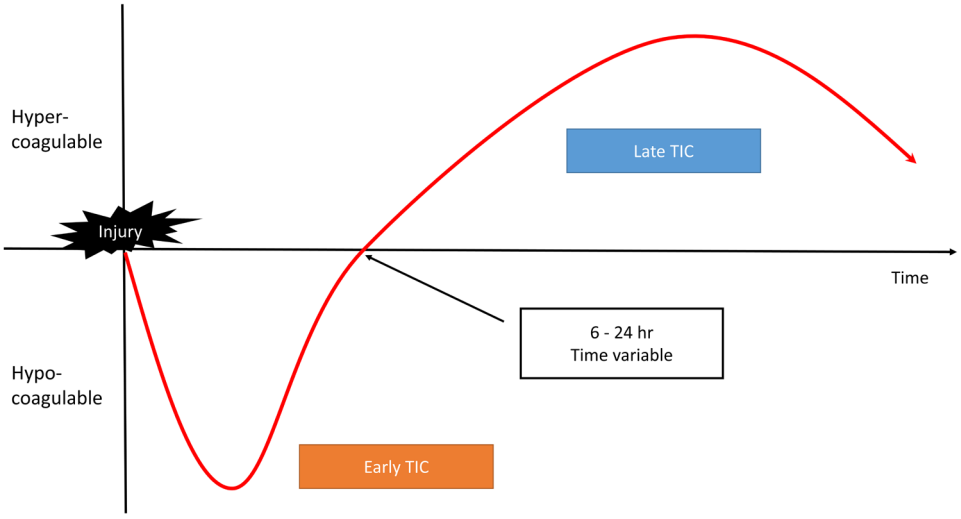

Figure 1. Time course of trauma-induced coagulopathy (TIC). Early TIC shows bleeding tendency, and late TIC shows a hypercoagulable status; transition timing is variable.

TIC is generally defined as trauma-induced changes in coagulation. Given the involvement of various underlying mechanisms, patients presenting with similar bleeding tendencies may necessitate individualized treatment strategies (Table 1). Research on TIC is ongoing, and current understanding and management strategies are expected to evolve.

PREHOSPITAL MANAGEMENT OF BLEEDING

Hemorrhagic shock is a major problem in trauma and also plays a key role in the development of TIC. Therefore, bleeding control, adequate perfusion, and management of hypocoagulopathy are the primary goals of initial management, which should be started immediately after injury. A tourniquet or manual compression at the bleeding site are typical and commonly effective for mechanical bleeding control. To enhance patient survival by bystander intervention prior to the arrival of healthcare providers, the "STOP the Bleeding" campaign in the United States aims to place bleeding control kits next to automated external defibrillator kits [7].

Crystalloid fluid has been recommended rather than colloids to maintain adequate perfusion. Albumin can be utilized in some cases, but hydroxyethyl starch is prohibited [8-10]. However, the administration of large volumes of crystalloids in the prehospital setting has been associated with poor outcomes [11], and such use has recently declined [12]. As a result, the use of blood products, which have long been considered in prehospital care, is receiving increased attention.

PREHOSPITAL MANAGEMENT OF TRAUMA-INDUCED COAGULOPATHY

Due to the lack of methods to identify the phenotype of TIC in the prehospital setting, the administration of blood products or pharmacologic agents is often empirical. As a result, the efficacy of prehospital interventions has shown considerable variability across studies. However, a large randomized controlled trial [13] demonstrated that the administration of tranexamic acid significantly reduced mortality in trauma patients without increasing the risk of vascular occlusive complications. Furthermore, tranexamic acid has been shown to improve survival in patients with traumatic brain injury [14]. A recent randomized study reported no significant improvement in functional outcomes at 6 months compared to placebo; however, it demonstrated a survival benefit at 24 hours and 28 days following injury [15]. Accordingly, the administration of tranexamic acid in the prehospital setting is becoming a global standard of care for trauma patients. However, it has not yet been implemented by emergency medical services in the Republic of Korea.

Whole blood transfusion was initially adopted during wartime, and its integration into military medicine occurred naturally. Although component therapy later became the standard, there has been a resurgence of interest in whole blood transfusion, particularly in the prehospital setting, where it has demonstrated favorable outcomes [16,17]. Therefore, efforts to expand its use beyond the military to civilian populations

Table 1. Evolution of the definition and understanding of TIC

	Past	Present
Terminology	Severe bleeding tendency Defibrination syndrome Acute traumatic coagulopathy	TIC
Cause	Bleeding	Tissue injury and shock
Mechanism	Consumptive loss of coagulation factors Dilutional effect by fluid and blood	Activation of the protein C pathway Impair thrombin generation Fibrinogen deficiency Platelet dysfunction Dysregulated fibrinolysis
Phenotype	Lethal triad: hypothermia Acidosis Coagulopathy	Early TIC: hypo-coagulopathy Late TIC: hyper-coagulopathy

TIC: trauma-induced coagulopathy.

are not unwarranted [18]. Nonetheless, despite its potential benefits, widespread implementation remains limited due to logistical and regulatory challenges in many countries. Even so, the clinical advantages of whole blood are increasingly recognized, prompting ongoing research into its use not only in prehospital care but also for in-hospital trauma resuscitation [19,20].

However, in the prehospital setting, alternative transfusion strategies and blood products have not been shown to be as effective as conventional methods. A 2017 systematic review [21] reported no survival benefit associated with the availability of prehospital red blood cells (RBCs). Subsequent retrospective studies suggested that, while prehospital RBC transfusion may reduce prehospital mortality and anemia, it did not significantly improve overall survival [22,23]. A randomized control trial [24] demonstrated a survival benefit of fresh frozen plasma (FFP) during aeromedical transport [25]. However, similar studies conducted in ground transport settings did not show a comparable survival advantage. Pusateri et al. [26] proposed that prehospital FFP may be beneficial when transport times exceed 20 minutes, based on analysis of two studies. Tucker et al. [27] reported that combined prehospital transfusion of FFP and RBCs was associated with improved 24-hour mortality compared to RBC transfusion alone, particularly in penetrating injuries. However, another randomized controlled trial [28] demonstrated no survival benefit of combined RBC and lyophilized plasma transfusion compared to 0.9% saline. Thus, the efficacy of prehospital transfusion remains inconclusive.

The administration of fibrinogen concentrate has also been explored. Although prehospital fibrinogen administration has been shown to improve clot stability [29], a meta-analysis failed to demonstrate a significant mortality benefit from early fibrinogen supplementation [30]. Nevertheless, early administration of fibrinogen has been found to significantly correct hypofibrinogenemia, a condition associated with increased mortality, warranting further investigation.

IN-HOSPITAL MANAGEMENT OF BLEEDING

According to Advanced Trauma Life Support (ATLS) guidelines [10], resuscitation should secure exsanguinous external bleeding control, airway, breath, circulation, disability, and the environment. Therefore, a secure airway and ventilator support are considered for shock patients, and large bore intravenous access should be achieved. In the context of damage control resuscitation, permissive hypotension has been proposed because achieving higher blood pressure often requires large volumes of fluid resuscitation or the use of vasopressors [3,31]. Moreover, elevated blood pressure may exacerbate bleeding by dislodging early clots or increasing the pressure at the bleeding site. According to the ATLS 11th edition [10], a systolic blood pressure around 90 mm Hg may be beneficial until definitive hemorrhage control is achieved. However, a higher systolic pressure may be appropriate in patients with head injury, spinal cord injury, or a history of hypertension. During permissive hypotension, frequent assessment of organ perfusion is required, and parameters such as laboratory findings, urine output, and skin perfusion (e.g., capillary refill) should be evaluated along with vital signs. To detect bleeding sources, chest, pelvic, and long bone radiographs, along with abdominal ultrasonography (focused assessment with sonography), are common. Computed tomography provides detailed information but may delay treatment and is not suitable for hemodynamically unstable patients. Once the bleeding source is identified, hemostatic measures should be executed if warranted. In conjunction with resuscitation efforts, early blood transfusion should be considered based on the severity of blood loss and the patient's hemodynamic status.

MASSIVE TRANSFUSION PROTOCOL

Massive transfusion is defined as the administration of more than 10 units of RBCs within 24 hours. A massive transfusion protocol (MTP) is designed to facilitate rapid and balanced delivery of blood products. Therefore, a predefined pack with a fixed ratio of blood products was developed to standardized and expedite transfusion in MTP. A large multicenter study [32] suggested that a platelets of FFP to RBC ratio less than 1:2 is associated with improved outcomes. Another randomized study [33] comparing a 1:1:1 ratio of platelets, FFP, and RBCs to a 1:1:2 ratio demonstrated similar overall mortality between two groups. However, the 1:1:1 group showed reduced mortality due to exsanguination. Therefore, a 1:1:2 ratio or higher is recommended in high-volume centers treating more severely injured patients. While multiple criteria have been proposed for MTP activation, its termination is generally guided by

confirmation of bleeding control and patient stabilization following adequate resuscitation [34]. A fixed ratio transfusion strategy (usually 1:1:1) is common in smaller hospitals regardless of laboratory findings. A meta-analysis demonstrated that an MTP resulted in a significant reduction in mortality and recommended its use in the management of major trauma [35]. The 1:1:1 transfusion strategy approximates the composition of whole blood, which led to the idea that direct transfusion of whole blood might be more effective, prompting renewed interest and research into the use of whole blood [36]. Studies [19,37,38] have demonstrated the effectiveness of such use, and there is a growing movement to adopt whole blood transfusion as an MTP.

GOAL-DIRECTED RESUSCITATION

Due to the nature of protocolized fixed-ratio transfusion, MTP carries a risk of unnecessary transfusion [39]. As over-transfusion can lead to serious complications [40], it is important to determine the appropriate volume for treatment. However, there has historically been no reliable method to measure TIC and to guide transfusion decisions. Although conventional coagulation tests are widely used, they are limited by delayed results (up to 60 minutes), reflect only early clot formation, and do not assess clot quality or platelet function [4]. Therefore, while laboratory-guided correction may be appropriate once the patient is stabilized, such tests are inadequate during the early phase of resuscitation. In this context, viscoelastic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have emerged as useful tools to provide more rapid and dynamic assessments of coagulation status and guide targeted transfusion strategies. Representative thresholds and targets used in goal-directed transfusion therapy are summarized in Table 2 [9,41-43]. Observational studies [44-47] have demonstrated improved outcomes and better prediction of transfusion requirements when using viscoelastic assays compared to conventional coagulation assays. Also, goal-directed therapy was associated with a reduced incidence of massive transfusion and a lower overall transfusion rate [48]. As a result, goal-directed therapy has become widely accepted in trauma resuscitation [9,49]. Although previous reviews [50-52] have shown that viscoelastic assays more accurately diagnose TIC, a recent systematic review [53] found no significant difference in mortality or thromboembolic events compared to conventional assays.

The implementation of goal-directed therapy has also shifted attention toward coagulation factor concentrates as targeted alternatives to traditional blood component therapy. Innerhofer et al. [54] reported that use of coagulation factor concentrates was effective and resulted in a reduction in transfusion requirements. Fibrinogen plays a key role in clot stability and cannot be adequately replaced by FFP alone. Therefore, numerous studies have investigated the early administration of fibrinogen using concentrate or cryoprecipitate, but the conclusions remain a subject of debate [55-58]. Despite this uncertainty, recent European guidelines [9] recommend the administration of fibrinogen concentrate or cryoprecipitate during the initial phase of management. A randomized trial investigating the early administration of prothrombin complex concentrate [59] attracted considerable attention but failed to demonstrate a significant reduction in 24-hour blood product requirements and instead reported an increased incidence of

Table 2. Suggested thresholds and targets for viscoelastic assay-based transfusion

TEG 6s		ROTEM	
CK-R >10 min	FFP 10–15 ml/kg PCC 20–25 IU/kg	EXTEM CT >80 sec	FFP 15 mL/kg PCC 20–25 IU/kg
CFF-MA <14 mm	Fibrinogen concentrate 3–6g Cryoprecipitate 2–4 U	FIBTEM CA10 <7 mm	Fibrinogen concentrate 3–6 g Cryoprecipitate 2–4 U
CRT-MA <50 mm	Platelet apheresis 1 U	EXTEM CA10 <40 mm	Platelet apheresis 1 U
CRT-MA <45 mm	Platelet apheresis 1–2 U		
CK LY 30 >2.6%	Tranexamic acid 15 mg/kg (max 1 g bolus)	EXTEM CT >APTEM CT	Tranexamic acid 15–20 mg/kg

ROTEM: rotational thromboelastometry; CK-R: kaolin reaction time; FFP: fresh frozen plasma ; PCC: prothrombin complex concentrate; EXTEM CT: extrinsic thromboelastometry – clotting time; CFF-MA: citrated functional fibrinogen-maximum amplitude; FIBTEM CA: fibrin-based thromboelastometry clot amplitude; CRT-MA: citrated rapid thromboelastography-maximum amplitude; EXTEM CA: extrinsic thromboelastometry clot amplitude; CK LY: kaolin lysis at 30 minutes; APTEM CT: antifibrinolytic thromboelastometry clotting time.

thromboembolic events.

FUTURE DIRECTION

As goal-directed therapy has gained increasing attention, the central issue has become identification of the proper approach— MTP or goal-directed therapy—in clinical practice. A randomized trial [43] comparing viscoelastic testing with conventional coagulation tests in patients undergoing MTP reported improved survival and reduced transfusion requirements in the goal-directed resuscitation group. However, a subsequent multicenter randomized trial [60] failed to show a significant reduction in 28-day mortality. Notably, a secondary analysis of this study [61] revealed that many bleeding trauma patients did not actually receive the indicated goal-directed treatment. Among those who did receive such therapy, lower mortality rates were observed. In a retrospective study, Prethika et al. [62] demonstrated that TEG-guided goal-directed transfusion resulted in decreased blood product use, reduced coagulopathy, and improved survival compared with conventional MTP. However, in the study by Paydar et al. [63], introduction of goal-directed therapy was associated with a reduction in transfusion volume but showed no improvement in survival. To date, the optimal strategy between fixed-ratio transfusion and goal-directed therapy remains controversial, as both have strengths and limitations (Table 3).

Although guidelines from both the European [9] and Eastern Association for the Surgery of Trauma in the U.S. [49] emphasize the importance of goal-directed therapy, there are notable differences in their approaches. In the United States, there is a growing trend toward early administration of whole blood, followed by additional factor concentrates or further transfusion decisions based on clinical assessment. In contrast, European practice often favors the early administration of RBCs and fibrinogen, with subsequent transfusion guided by viscoelastic assay results. These strategies may vary depending on institutional resources, the availability of blood products, and access to point-of-care testing. Notably, MTPs are not entirely excluded in European practice as they can be complemented by viscoelastic assays to identify specific deficiencies and guide the supplementation of targeted factor concentrates. Hence, goal-directed therapy is expected to remain a central component of trauma resuscitation. However, further research is needed to determine whether initial whole blood or MTP administration is superior to early initiation of RBCs combined with goal-directed therapy.

OTHER CONSIDERATIONS

With the development of novel antithrombotic agents, traditional drugs such as aspirin and warfarin are increasingly being replaced by newer alternatives. As these agents may increase bleeding tendencies, it is essential to identify and review patient medication history. Although specific reversal agents for some of these drugs are available, their use can be limited by factors such as cost and accessibility. In such cases, correction based on viscoelastic assays may offer a viable alternative. However, in Korea, the availability of certain coagulation factors remains limited, which poses challenges in implementing appropriate correction strategies.

Although primary tissue injury directly contributes to the development of TIC, secondary effects can exacerbate the condition. Therefore, the components of the traditional "lethal triad" of hypothermia, acidosis, and coagulopathy must be corrected aggressively. Hypocalcemia, which is frequently observed during massive transfusion, has also been associated with poor clinical outcomes. As a result, the concept of the “diamond of death” has emerged, incorporating hypocalcemia as a fourth critical component alongside the lethal triad [64]. Rapid assessment of serum calcium levels and early adminis-

Table 3. Comparison between fixed ratio transfusion versus goal-directed therapy

	Fixed ratio transfusion	Goal-directed therapy
Approach	Empiric	Individualized
Advantage	· Rapid (does not require laboratory results)	· Tailored therapy with optimized component ratios
	· Easy to standardize protocol	· Detects hyperfibrinolysis not recognized by fixed-ratio transfusion
	· Mimic composition of blood lost during hemorrhage	· Enables targeted factor replacement
Disadvantage	· Risk of over-transfusion	· Requires specialized equipment
		· Potential delay in transfusion initiation

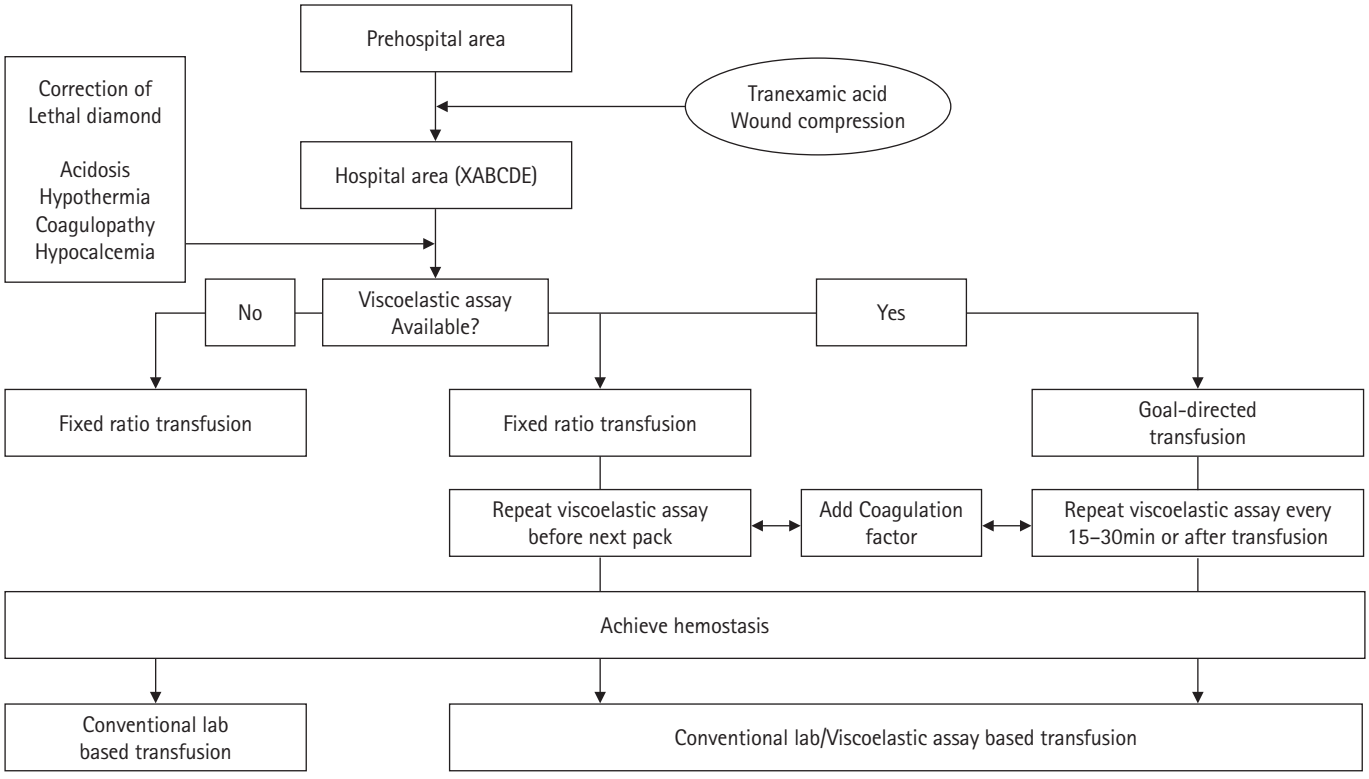

Figure 2. Potential hemostatic strategies. xABCDE: exsanguinous bleeding control/airway/breath/circulation/disability/environment).

tration of calcium should be considered in the management of trauma patients, particularly those undergoing massive transfusion.

CONCLUSIONS

Hemostatic resuscitation has become a cornerstone in modern trauma care, encompassing both prehospital and in-hospital strategies. Early interventions, including tourniquet application and administration of tranexamic acid or whole blood, are recommended in the prehospital setting and may improve outcomes. In the hospital, while fixed-ratio MTPs remain widely used, they carry a risk of over-transfusion. Goal-directed therapy guided by viscoelastic assays allows individualized transfusion strategies and has shown potential in improving outcomes. The early use of coagulation factor concentrates, particularly fibrinogen, further supports targeted correction of coagulopathy. Although challenges remain in implementation, goal-directed therapy is expected to play an increasingly central role, and future research should focus on optimizing both prehospital and in-hospital approaches to TIC.

The potential hemostatic strategies are summarized in Figure 2.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Junsik Kwon https://orcid.org/0000-0003-3164-4995
Byung Hee Kang https://orcid.org/0000-0003-3204-3251

AUTHOR CONTRIBUTIONS

Data curation: BHK. Visualization: BHK. Writing - original draft: JK, BHK. Writing - review & editing: BHK. All authors read and agreed to the published version of the manuscript.

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